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Isolated nonspecific terminal ileitis: prevalence, clinical evolution and correlation with metachronous diagnosis of Crohn's disease: a retrospective study and review of the literature

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Abstract

Background The existing literature does not provide adequate guidance on the diagnosis and management of patients with nonspecific terminal ileitis, while data regarding the percentage of patients who ultimately develop Crohn's disease (CD) are scarce. We evaluated the prevalence and natural course of nonspecific terminal ileitis in patients who underwent colonoscopy during a 11-year period.

Methods All patients with endoscopic findings of terminal ileitis and nonspecific histological findings were included. Exclusion criteria were a clinical history of CD or any other disease that can cause terminal ileitis, or a recent history of using drugs implicated in lesions of the terminal ileum.

Results From 5353 colonoscopies, 92 patients with nonspecific terminal ileitis were identified (prevalence: 1.7%). Among these patients, 56 (61%) had available follow up for ≥6 months after the initial endoscopy. Main indications for endoscopy were chronic diarrhea (37.5%), screening endoscopy (23%), and abdominal pain (20%). Sixteen (29%) patients received medical treatment, while recession of symptoms was recorded in 19 of 43 symptomatic patients (44.1%). Twenty-three (41%) of the 56 patients underwent a second endoscopy and 15 (65.2%) cases had persistent endoscopic findings. Eleven (19.6%) of the 56 patients were eventually diagnosed with CD. The probability of CD diagnosis was significantly higher in patients with persistent symptoms (P=0.002) and endoscopic findings at follow up (P=0.038).

Conclusions Nonspecific terminal ileitis generally has a benign clinical course. However, patients with persistent symptoms and endoscopic lesions are at increased risk for subsequent development of CD.

Keywords Nonspecific terminal ileitis, Crohn's disease, colonoscopy

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Introduction

Intubation of the terminal ileum is performed quite often during colonoscopy, even in asymptomatic patients, and is encouraged in patients with symptoms such as diarrhea, abdominal pain, or anemia. Occasionally, individuals without a history of a specific bowel disease may present incidentally with isolated mild ileitis. According to the current literature, 0.3-6.8% of asymptomatic patients who undergo screening colonoscopy are diagnosed with nonspecific terminal ileitis [1-5], although a significantly higher prevalence (63%) of abnormal endoscopic findings was reported in one study [6]. Apart from Crohn's disease (CD), terminal ileitis is attributed to various different causes [7]. It may be related to drugs, in particular nonsteroidal anti-inflammatory drugs (NSAID) [8-10], intestinal infections [11-14], vascular disorders [15,16], and neoplasms [17-19], or may rarely occur in the context of spondyloarthropathies [20] and infiltrative diseases [21,22]. The term "nonspecific terminal ileitis" is used for cases in which a

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definite cause of isolated terminal ileitis cannot be identified and ileal biopsies do not lead to a specific diagnosis [23,24].

The main question is whether isolated terminal ileitis of undefined origin predisposes to the development of CD. In addition, the possibility of an underlying, unrecognized CD or its early appearance has to be taken into account, thus rendering further evaluation and follow up necessary. Based on limited data, the rate of progression of nonspecific mild terminal ileitis to clinically impactful CD appears to be low, and depends on the synchronous existence of symptoms and elevated inflammatory markers such as C-reactive protein (CRP) and fecal calprotectin (FCP) [25-28].

Given the possibility of progression of nonspecific isolated terminal ileitis to CD, especially in asymptomatic patients, it is important to recognize disease characteristics that predispose to or predict this progression. Such a distinction would aid in the determination of a high-risk group, thus avoiding further diagnostic workup and possible unwarranted treatments, as well as reducing patients' anxiety. Until now, there have been no formal guidelines to orientate clinicians in the evaluation of patients with isolated nonspecific terminal ileitis, although algorithms have been proposed by some authors, focusing on the importance of intestinal and extraintestinal symptoms, as well as on the presence of elevated inflammation markers and/or small bowel imaging abnormalities [29].

In consideration of the availability of limited and conflicting data, mainly from small series of patients with short follow up, we undertook a thorough analysis of the endoscopic and histological findings in relation to the clinical course of symptomatic and asymptomatic patients with nonspecific isolated terminal ileitis. The main purpose was to assess any possible association between this nonspecific entity and a metachronous diagnosis of CD.

Patients and methods

We retrospectively reviewed the medical, endoscopic and histological reports of all patients diagnosed with isolated terminal ileitis after colonoscopic examination performed from January 2008 to December 2018 at the Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, "Laiko" General Hospital of Athens. The study protocol complied with all ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki.

Terminal ileitis was defined as mucosa erosions, ulcerations, edema or erythema in the terminal ileum at the time of endoscopy. The following exclusion criteria were applied: clinical history of CD or ulcerative colitis; recent (<6 months) intake of NSAID or other drugs implicated in terminal ileum injury; diseases that are known to affect the terminal ileum, such as infections, infiltrative and vascular disorders; and when ileal histology was diagnostic for a specific entity to which terminal ileitis could be attributed. After baseline data collection, all patients with nonspecific isolated terminal ileitis were scheduled for a follow-up phone visit, which took place in January 2019. The predefined questionnaire focused on whether the patients had undergone follow-up endoscopy at least 6 months later, with biopsy, including available results or any other evaluation procedure relating to the existence of symptoms during or subsequent to the examination period, and on drug history with special reference to any relevant treatment administration. Information regarding any disease manifestation or bowel surgery up to the date of the phone visit was also recorded. The minimum interval between the first and second endoscopy was chosen to be 6 months, in order to evaluate probable endoscopic and histological healing. In particular, for asymptomatic patients with nonspecific terminal ileitis, 6 months was considered to represent an acceptable time interval before repeating the endoscopy.

Besides the phone visit, data concerning the patients' medical history, including information on NSAID use and prior infectious diseases, were also retrieved from the endoscopic reports, in which the reason for the endoscopy and a brief medical history were listed.

Histological evaluation

Histological examination of the biopsy material from the terminal ileum was performed by 2 experienced pathologists, who reached agreement on the evaluation of each case. Nonspecific changes (mild chronic inflammation, edema and lymphoid hyperplasia) and findings of terminal ileitis were recorded. Terminal ileitis activity of mild and moderate severity was determined by the presence of neutrophils in the *lamina propria*, cryptitis and crypt abscesses, whereas severe activity was characterized by the presence of erosions and ulcerations. Chronicity changes included fibrosis, architectural alterations, and pseudopyloric metaplasia.

Statistical analysis

Statistical analysis was performed using the software SPSS Statistics for Windows (Version 28.0, IBM Corp Armonk, NY, USA). Data were expressed as frequencies, mean ± standard deviation (SD), or median with interquartile range (IQR), as appropriate. Quantitative variables were compared using Student's t test or the Mann-Whitney test for normally distributed and non-normally distributed variables, respectively. Qualitative variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The relationships between quantitative variables were assessed by Spearman's correlation coefficient. Kaplan-Meier curves were used to assess the probability of CD diagnosis over time. Cox regression analyses were performed in order to identify factors predictive of CD diagnosis, and hazard ratios (HR) with their 95% confidence intervals (CI) were calculated. Only parameters with significant ($P<0.05$) or a trend towards significant ($P<0.10$) associations with the dependent variable in the univariate analyses were included in the multivariate analysis models. All tests were 2-sided.

Results

From 5353 lower gastrointestinal endoscopies performed between 2008-2018, 92 patients were identified to have nonspecific terminal ileitis (prevalence: 1.7%). Their mean age was 50±16 years, 52 (56.5%) were males and 67 (72.8%) were symptomatic. Among these patients, 56 (61%) had available follow-up information for at least 6 months after the initial endoscopy; they comprised the patient population of our study. The main characteristics of these 56 patients are presented in Table 1.

Clinical features

Most of the 56 patients (76.8%) were symptomatic when presenting for initial endoscopy. Chronic diarrhea was the prevailing symptom (37.5%), while 13 (23.2%) patients underwent screening endoscopy without reporting any symptoms.

Extraintestinal manifestations were reported by 6 patients. Of these, 4 had ankylosing spondylitis (2 symptomatic and 2 asymptomatic), 1 nodular erythema and 1 anemia (both symptomatic). The incidence of extraintestinal manifestations did not differ between the initially symptomatic and asymptomatic patients (5/43 or 11.6% vs. 1/13 or 7.7%, P=0.598).

Endoscopic and histological features

The endoscopic findings included mucosa erosions or ulcers (37/56 or 66%), mucosa edema (14/56 or 25%) or erythema (9/56 or 16%). Histological examination revealed nonspecific findings in all patients, regardless of the endoscopic features. The most common histological findings were nonsignificant changes, including mild chronic inflammation, edema and lymphoid hyperplasia. In particular, histological examination revealed the following diagnostic subgroups: nonsignificant changes (23 cases), mild focal or segmental chronic active ileitis (12 cases), mild focal or segmental chronic active ileitis with chronicity changes (6 cases), chronic ileitis with severe activity (7 cases), chronicity changes without inflammatory activity (4 cases), and chronic ileitis with severe activity and changes of chronicity (4 cases). Notably, no patient had granulomas in the histological reports of the terminal ileum.

Table 1 Main characteristics of 56 patients with nonspecific terminal ileitis

Characteristics	Value
Age, mean ± SD years	50 ± 16
Male sex, n (%)	32 (57.1)
Symptomatic patients, n (%)	43 (76.8)
Reason for endoscopy, n (%)	
Chronic diarrhea	21 (37.5)
Screening for colon cancer	13 (23.2)
Abdominal pain	11 (19.6)
Iron deficiency	6 (10.7)
History of partial ileus	3 (5.4)
Rectal bleeding	1 (1.8)
Anal fissure	1 (1.8)
Treated patients, n (%)	16 (29.0)
Type of treatment among 16 treated patients, n (%)	
Budesonide	8 (50.0)
Conventional corticosteroids	4 (25.0)
Aminosalicylates	4 (25.0)
Antibiotics	2 (12.5)
Follow-up endoscopy, n (%)	23 (41.1)

SD, standard deviation

Imaging and endoscopic procedures

Fourteen of the 56 patients (12 symptomatic and 2 asymptomatic) underwent further evaluation with magnetic resonance enterography (MRE). Among the 12 symptomatic patients, 7 had abnormal findings on MRE, mainly consisting of mural thickening, 2 also had stenosis in the terminal ileum with prostenotic dilation, and 1 had stenosis in the duodenum; the latter patient underwent enteroclysis, in which aphthous ulcers in the terminal ileum were detected. Of the 2 asymptomatic patients, one had no abnormal finding and the other had mural thickening. Five symptomatic patients underwent computed tomographic enterography (CTE); all had edema and mural thickening of the terminal ileum. In addition, 1 patient also had an enterovesical fistula and 1 had stenosis of the terminal ileum. Additionally, 8 (7 symptomatic and 1 asymptomatic) patients were evaluated with computed tomography (CT). Only 2 symptomatic patients had mural thickening in the terminal ileum, while CT did not reveal any abnormal finding in the other 6 patients. Three symptomatic patients were also evaluated with video capsule endoscopy, which showed findings of inflammation of the terminal ileum in 2 of them.

Four symptomatic patients underwent upper gastrointestinal endoscopy for upper gastrointestinal symptoms. Gastritis was found in all (2 were *Helicobacter pylori* positive). Interestingly, one of these patients had granulomas in biopsies from the antrum, but not from the terminal ileum, and was finally diagnosed with CD, also having elevated FCP and CRP as well as a history of nodular erythema.

Laboratory data

CRP was elevated (>5 mg/L) in 20 (80%) of 25 initially symptomatic patients and in 2 (50%) of 4 asymptomatic patients (P=0.238). Ten symptomatic patients had an available FCP measurement, which was elevated (>50 μg/mg) in 4 of them. In fact, all 4 patients had FCP >200 μg/mg and elevated CRP. High calprotectin (>200 μg/mg) with normal CRP was found in the one asymptomatic patient who had such measurements available.

Treatment for terminal ileitis

Of the 56 patients with nonspecific terminal ileitis, 16 (29%) received various types of treatment, aiming to achieve a clinical or endoscopic response (Table 1). Administration of treatment was more frequent in symptomatic (15/43 or 34.8%) compared to asymptomatic patients (1/13 or 7.7%, P=0.018). The only asymptomatic patient who received treatment was a 61-year-old male patient with abnormal MRE findings in the distal ileum. Budesonide (50%), conventional corticosteroids (25%) and aminosalicylates (25%) were the most frequent therapeutic choices, while 2 patients (12.5%) received antibiotics (one ciprofloxacin and the other azithromycin) (Table 1). Three patients received combination therapy (budesonide plus aminosalicylates, aminosalicylates plus corticosteroids, and corticosteroids plus antibiotics).

Clinical course

The mean duration of follow up was 45±33 months. In total, 22 of the 56 patients (39.3%) were symptomatic during follow up. Nineteen (44.1%) of the 43 initially symptomatic patients had persistent symptoms and 3 (23.1%) of the 13 initially asymptomatic patients developed symptoms during follow up. Among the 16 patients who received any type of treatment, 14 (87.5%) remained symptomatic during follow up, perhaps because treatment was administered to the patients with more severe clinical presentations. The only asymptomatic patient who received treatment after the initial endoscopy did not report any symptoms during follow up.

Follow-up endoscopy

Repeat endoscopy, at least 6 months after the initial examination, was performed in 23 (41.1%) of the 56 patients. Among 43 patients who were symptomatic at presentation, 19 (44.2%) underwent a second endoscopy, while 4 (30.8%) of the 13 asymptomatic patients were also examined. Fourteen of the 23 (60.8%) patients who underwent repeat endoscopy were symptomatic at the time of the second endoscopic examination. Persistent abnormal endoscopic findings were reported in 15 of 23 (65.2%) patients. Among these 15 patients, 11 (73.3%) were symptomatic at the time of follow-up colonoscopy. New biopsies were taken from the terminal ileum in all patients.

Clinical outcome

CD was eventually diagnosed in 11 (19.6%) of the 56 patients. The mean time to CD diagnosis was 18±17 months. More specifically, CD was diagnosed in 9 (20.9%) of the 43 initially symptomatic and in 2 (15.4%) of the 13 initially asymptomatic patients (P=0.501). Moreover, CD was diagnosed significantly more frequently in patients with persistent symptoms (9/19 or 47.3%), compared to those who were asymptomatic during follow up (2/34 or 5.9%, P=0.002). An ultimate diagnosis of CD was more frequent in patients with extraintestinal manifestations, compared to patients without (4/6 or 67% vs. 7/50 or 14%, P=0.011). Similarly, a CD diagnosis was significantly more frequent in patients with persistent endoscopic findings, compared to patients without (9/15 or 60% vs. 1/8 or 12.5%, P=0.038).

Considering the initial histological profile of the patients who were finally diagnosed with CD, there were 2 of 23 (8.6%) cases with non-significant changes, 3 of 12 (25%) cases with mild focal active or segmental chronic active ileitis, 2 of 6 (33.3%) cases with mild focal active or segmental chronic active ileitis with chronicity changes, 1 of 7 (14.3%) cases with chronic ileitis with severe activity and 3 of 4 (75%) cases with chronic ileitis with severe activity and changes of chronicity.

All symptomatic patients and 1 asymptomatic patient with abnormal MRE findings, as well as 2 of the symptomatic patients with abnormal findings in CTE, were eventually diagnosed to have CD.

The diagnosis of CD in 1 patient without endoscopic findings at follow-up examination was based on compatible histological lesions, and MRE findings showing stenotic areas with prostenotic dilations in the ileum, along with elevated CRP and FCP. Moreover, 1 patient with persistent symptoms was diagnosed to have CD, based on upper gastrointestinal endoscopic and histological findings. Interestingly, from the patient group that exhibited constant endoscopic findings, 1 patient was finally diagnosed with intestinal endometriosis and another with systemic lupus erythematosus affecting the small bowel.

Patients with elevated FCP tended to be more frequently diagnosed with CD compared to patients with normal FCP (P=0.08). Interestingly, 4 of the 5 patients with elevated FCP were finally diagnosed to have CD after further imaging evaluation. In contrast, elevated CRP was not found to be associated with the final diagnosis of CD in patients with nonspecific terminal ileitis (P=0.204). In Cox regression analysis, a subsequent CD diagnosis was associated with persistent symptoms after the initial evaluation (HR 6.333, 95%CI 1.311-60.588; P=0.022), but not with the presence of symptoms at the initial diagnosis of ileitis (P=0.266) (Fig. 1). In addition, no association was found between the type of symptoms and the development of CD.

Discussion

The natural history and clinical course of nonspecific terminal ileitis remain unclarified. In the current study, we retrospectively reviewed 5353 colonoscopies and identified 92 (1.7%) cases with nonspecific terminal ileitis, suggesting that this entity is relatively rare in routine clinical practice. CD was subsequently diagnosed in 20% of our patients with nonspecific terminal ileitis and available follow up, with a non-significant difference (21% vs. 15%) between cases with and without symptoms on the initial colonoscopy. More importantly, CD was diagnosed more frequently in patients with persistent symptoms, compared to those who were asymptomatic during follow up. The persistence of symptoms

after the diagnosis of nonspecific terminal ileitis was found to be the only independent prognostic factor for subsequent development of CD. In addition, almost 80% of our patients with persistent symptoms who underwent follow-up endoscopy had persistent endoscopic lesions, while approximately two thirds of them were diagnosed with CD. Thus, persistent symptoms in patients with nonspecific terminal ileitis should stimulate a closer follow up and especially a more extensive work-up.

On the histological level, different subgroups with variable prognostic value were recognized. Although the limited number of cases does not permit definite conclusions, there are indications that combined features of inflammatory activity and chronicity define a diagnostic risk group that may already harbor CD.

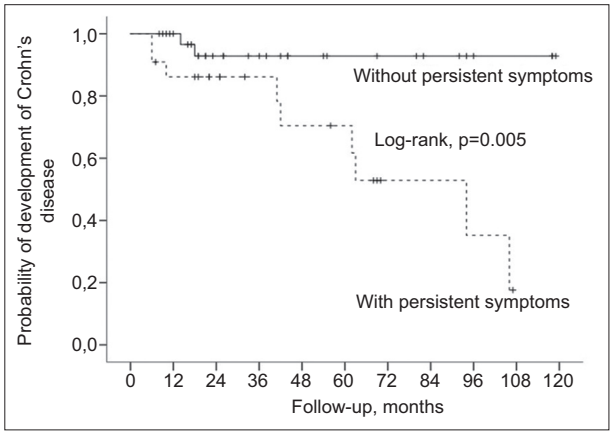

Figure 1 Probability of development of Crohn's disease according to the persistence of symptoms after the initial evaluation of patients with nonspecific isolated terminal ileitis (Kaplan-Meier curves)

Additional evaluation procedures seem to be of great importance in some of these patients. Although guidelines are still lacking, a stepwise approach, with FCP measurement and further imaging examinations in the case of elevated FCP, seems to be a reasonable strategy, especially in symptomatic patients. Findings of stenoses or fistulae in the imaging procedures, along with abnormal inflammatory markers, may support a diagnosis of CD, even if histology is inconclusive. Moreover, the presence of extraintestinal manifestations that could be possibly related to CD should be thoroughly assessed. Since there is a possibility of an underlying undiagnosed CD, or of early development of CD, careful further evaluation and close follow up are mandatory.

Our results are in agreement with most studies from western countries, which suggest that at least 1 of 5 symptomatic patients with nonspecific terminal ileitis will eventually be diagnosed with CD, in contrast to a small proportion of asymptomatic cases (Table 2).

In an Italian prospective study [28], 10 (20%) of 51 symptomatic patients with nonspecific ileitis were diagnosed with CD, a rate analogous to that observed in our investigation. Similarly, in a study from Ireland [30], 14% of 63 patients with isolated active ileitis (including cases with normal biopsies and/or NSAID intake) developed CD by a median follow up of 40 months. Interestingly, individuals with isolated active ileitis were found to share an excess of *NOD2* mutations with CD patients.

An older study from the USA [31], including 40 patients with ulcerative ileitis, reported no progression to a specific disease during a median follow up of 3.2 years. Thirty-three of these patients, however, had a history of NSAID intake, and

Table 2 Main published studies including patients with nonspecific terminal ileitis

1st Author [ref.], year	Type of study	Country	Patients, n	Asymptomatic/ symptomatic patients	Mean/median follow up, months	Rate of Crohn's disease diagnosis
Bezzio [28], 2017	Prospective	Italy	51	0/51	15	19.6%
O'Donnell [30], 2013	Prospective	Ireland	63	3/60	40	14% (in 43 patients with available follow up)
Lengeling [31], 2003	Retrospective	USA	40	25/15	27	0%
Goldstein [32], 2006	Retrospective	USA	28	0/28	70	29%
Tse [33], 2017	Retrospective	USA	108	0/108	55	4,6%
Chang [27], 2010	Retrospective	Korea	93	93/0	30	1.1%
Wang [35], 2011	Retrospective	China	7	1/6	84	0%
Fangbin [36], 2014	Retrospective	China	34	3/31	36	23.5% (asymptomatic 0%, symptomatic: 26%)
Kedia [37], 2016	Prospective	India	45	0/45	14	89.5% (17/19 symptomatic patients with nonspecific inflammation)
Courville [26], 2009	Retrospective	Lebanon	29	14/15	asymptomatic: 64, symptomatic: 84	asymptomatic: 0%, symptomatic: 67% (histological chronicity: 80%, focal active ileitis: 40%)
Lervatorvsky [38], 2022	Retrospective	Israel	488	0/488	75	3.9%

most of them were asymptomatic. A rate close to our results was observed in another American survey, after evaluation of 28 patients with mild bowel habit alterations and small terminal ileum aphthous erosions on colonoscopy (4 patients reported NSAID intake), 29% of whom developed CD after a mean follow up of 3.6 years [32]. In contrast, in a series of 108 symptomatic patients with terminal ileitis followed for a median of 55 months, CD was diagnosed in 4.6% of cases, a rate lower than usual in western studies [33]. Similarly to our results, there was no association between types of symptoms and diagnosis of CD. Bowel wall narrowing or stricturing on abdominal imaging were proposed as predictive factors of progression of isolated active terminal ileitis to CD [33].

Studies from East and West Asia show differences in their results. In a study from Korea [27], CD was diagnosed in 1.1% of 93 patients with asymptomatic terminal ileitis during a median follow up of 30 months. Moreover, only 31 of the 93 patients again showed terminal ileitis at the follow-up endoscopy. The low rate of CD diagnosis may be associated with the inclusion of exclusively asymptomatic patients and the low overall prevalence of CD in South Korea in comparison to western countries [34]. In a study from China [35], none of 7 patients with small bowel ulcers on ileocolonoscopy or enteroscopy developed CD during a 5-year period. In contrast, in another Chinese study [36], 8 (23.5%) of 34 patients with terminal ileitis were finally diagnosed with CD during a mean follow up of 3 years. Abdominal pain was significantly associated with the development of CD, whereas patients without abdominal pain had a high likelihood of mucosa healing. Endoscopic and histological findings did not seem to predict the disease outcome.

In a study from India [37], including 45 symptomatic patients with terminal ileitis, the absence of significant clinical features, the presence of superficial ulcers on endoscopy and nonspecific histological findings were reported to rule out the possibility of any significant diagnosis such as CD. In a study from Lebanon [26], none of 14 asymptomatic patients with terminal ileitis was diagnosed with CD during a follow up of 2.2-12.6 years, although features of chronicity were reported histologically in 11 of them. On the other hand, 80% of symptomatic patients with histological chronicity developed CD. The authors concluded that the presence of symptoms, rather than the histological findings, is the strongest predictor of CD development. The high rate of ultimate CD diagnosis in this study may be explained by the long follow-up period and the selected patient population with histological findings of chronicity. Finally, a recent retrospective study from Israel [38] reported a low overall risk (4.7%) for subsequent development of inflammatory bowel disease in patients presenting with symptoms and/or signs of ileitis or colitis during a 9-year follow-up period.

It should be noted that the reviewed studies did not extensively evaluate the value of noninvasive inflammatory factors, such as FCP, as prognostic markers of the future evolution of terminal ileitis to CD. One study [28] excluded patients with elevated CRP, whereas CRP elevation was not associated with the diagnosis of CD in another study [33]. However, a trend for higher CRP values was found in patients who developed inflammatory bowel disease.

This is the first study in the Balkans that addresses the clinical importance and outcome of nonspecific isolated terminal ileitis, placing emphasis on its association with a subsequent CD diagnosis. The strengths of our study include the incorporation of several additional examinations and the determination of inflammatory markers, such as CRP and FCP, in a large proportion of our patients, and the histological evaluation of the ileal biopsies by 2 experienced pathologists. However, there are also some limitations to be considered, such as our inability to make contact with all patients who were initially found to have terminal ileitis according to our endoscopy reports. Moreover, our study sample was relatively small, and only a proportion of the patients underwent repeated ileocolonoscopy. We assumed that the possibility for additional patients to develop CD was negligible, since they had continued healthcare follow up, even if they did not repeat the colonoscopy. Various types of treatment were given to a proportion of our 56 patients, but such a heterogeneous management is to be expected, even from doctors of the same department, since there are no clinical guidelines or clear expert recommendations for patients with nonspecific ileitis.

In conclusion, the findings of this retrospective study suggest that, in the absence of symptoms, the risk of CD is low among patients with nonspecific isolated terminal ileitis. However, persistent symptoms in such patients are associated with a substantial risk for subsequent CD diagnosis. Moreover, the combined histological pattern of inflammatory activity and chronicity changes may prove to be of diagnostic significance. Larger studies with a longer follow up, as well as assessment of surrogate inflammatory markers, may contribute to a better characterization of the subgroups of patients with nonspecific isolated terminal ileitis who need further diagnostic workup, aiming to optimize their management.

Summary Box

What is already known:

- The natural history and clinical course of nonspecific terminal ileitis has not been defined
- Nonspecific terminal ileitis can be found incidentally in asymptomatic patients
- Nonspecific terminal ileitis seems to have a generally benign course

What the new findings are:

- Patients with nonspecific terminal ileitis and persistent symptoms have a higher risk for development of Crohn's disease
- Most patients with nonspecific terminal ileitis and persistent symptoms who develop Crohn's disease also have persistent endoscopic lesions
- Persistent symptoms in patients with nonspecific terminal ileitis should stimulate a closer follow up

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